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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/748,094	12/31/2003	Gautam Vinod Daftary	067080-0003	6940

25269 7590 03/09/2011

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EXAMINER	
KISHORE, GOLLAMUDI S	

ART UNIT	PAPER NUMBER
1612	

MAIL DATE	DELIVERY MODE
03/09/2011	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)
	10/748,094	DAFTARY ET AL.
	Examiner	**Art Unit**
	Gollamudi S. Kishore, Ph.D	1612

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2011*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10,12,14-22 and 63-69* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8, 10, 12, 14-22 and 63-69* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)

2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.

4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .

5) ☐ Notice of Informal Patent Application

6) ☐ Other: _____.

DETAILED ACTION

The amendment, power of attorney and the assignee showing the ownership all filed on 1-5-11 are acknowledged.

Claims included in the prosecution are 1-8, 10, 12, 14-22 and 63-69.

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 69 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

It is unclear as to what applicant intends to convey by "at least 25 times longer than conventional ***non-liposomal*** formulations when tested in Swiss albino mice at equivalent doses. When a liposomal formulation is tested with a ***non-liposomal formulation***, it is natural for the liposome formulation to have a longer circulation times because liposomes are sustained release vehicles. Furthermore, what is being tested? Phospholipid, cholesterol mixture?

Applicant's lengthy arguments have been fully considered, but are not persuasive. In essence applicant argues that one of ordinary skill in the art would understand that is a normal comparison would clearly understand the meets and bounds of the invention and what the applicants have defined as their invention. Applicant points out to Table 1 and Example IV which apparently discuss the drug 'doxorubicin' and thus, according to applicants the term is defined in the specification.

On page 5, applicant states the following: "wherein the non-PEGylated doxorubicin liposomes have a circulation time in blood at least 25 times longer than that obtained with ADRIAMYCIN when tested in Swiss albino rats".

These arguments are not persuasive. First of all claim 1 does not recite doxorubicin as the active agent. In fact, claim 1 does not recite any active agent. Secondly, Adriamycin is a solid and one can make different forms of non-liposomal compositions such as emulsions and even other non-liposomal sustained release formulations. Similar is the case with different drugs administered in medical field. The rejection is maintained.

Claim Rejections - 35 USC § 103

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

4. Claims 1-8, 10, 12, 14-22 and 63-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hong (Clinical Cancer Research, 1999) of record, Janoff (4,880,635) and Papahadjopoulos 4,235,871) optionally in further combination with Barenholz (5,316,771).

Hong teaches a direct comparison of liposomal doxorubicin with or without polyethylene glycol coating. ***According to Hong, "Paradoxically, the group of mice***

treated with liposomal doxorubicin without PEG had higher tumor doxorubicin concentrations" (Abstract). The method of preparation involves the preparation of a lipid film containing DSPC and cholesterol and the hydration of these lipids using ammonium sulfate solutions. Although pH of these solutions is indicated, it is unclear whether buffers are used to prepare the ammonium sulfate solutions in Hong. Doxorubicin was loaded into the liposomes by remote loading (abstract and Materials and Materials and Methods) and therefore, the removal of external ammonium sulfate for this loading is implicit in Hong. What is also lacking in Hong is the use of sucrose and histidine in the hydration buffer. Also unclear from Hong as to how much hydration buffer is added. However, since to form liposomes sufficient hydration of the lipids is important, it would have been obvious to one of ordinary skill in the art to determine as to how much hydration buffer is needed for complete formation of liposomes.

Papahadjopoulos discloses methods of formation of liposomes. The methods involve either removal of the organic solvent before hydration (Example 1) or making an emulsion using an organic solvent containing phospholipid and an aqueous medium and evaporating the organic solvent (Example 2). In either method, the amount of the lipid is 100 micromoles and the aqueous medium added is 1.5 ml which corresponds to 15 ml of aqueous medium per millimole of the phospholipid.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (Example 1; col. 21, line 23 through col. 21, line 27). Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole).

Barenholz teaches a method of creating an ammonium sulfate gradient in liposomes to load active agents into liposomes. The method involves hydrating the lipid film with ammonium sulfate and removal of the external ammonium sulfate followed by loading of the amphipathic active agent. According to Barenholz, effectively removing the outside ammonium by methods used and recognized in the art, in particular, dilution, gel exclusion, dialysis and diafiltration (abstract, col. 6, lines 10-38, columns 9 and 10 and examples).

It would have been obvious to one of ordinary skill in the art to include sucrose and histidine in Hong since Janoff teaches that sucrose protects the liposomes during the dehydration/rehydration process and Papahadjopoulos teaches the routine practice of the inclusion of histidine in the hydration buffer. The removal of external ammonium ions by dialysis in Hong would have been obvious to one of ordinary skill in the art since such a removal results in the formation of ammonium gradient for the subsequent loading of active agents as taught by Barenholz.

Applicant’s arguments have been fully considered, but are not found to be persuasive.

Applicant argues that Hong is deficient in at least two elements in the claims: 1) an aqueous medium consisting essentially of ammonium sulfate and sucrose and 2) removing extra liposomal hydration salt from the liposomal composition using a sucrose-histidine buffer solution.

These arguments are not persuasive since the reference of Papahadjopoulos shows the routine use of histidine buffer for hydrating the lipids and Janoff teaches why

sucrose should be used in the hydration buffer. Applicant not shown any unexpected results by using the art known hydration buffer and sucrose in the hydrating medium.

Applicant argues that Hong teaches using PEGylated liposomes to prolong liposome circulation and thus Hong's liposomes results in the problems that the instant invention solves by not using PEGylated liposomes, such as Hand and Foot syndrome.

This argument is not persuasive since as pointed out before, Hong teaches the preparation of liposomal compositions with and without PEG as the title itself indicates and instant claims are drawn to a method of preparation and the product (see also Materials and Methods and Figures 1-4) and not method of increasing the circulation times without PEG.

Applicant argues that Hong does not teach the following:

> (1) removing the solvent or mixture of solvents and adding an aqueous hydration media to the phospholipids and sterols; or
>
> (2) adding an aqueous hydration media to the phospholipids and sterols in the solution; and removing the solvent or mixture of solvents;
>
> (3) removing ammonium sulphate from extra liposomal hydration medium by dialysis using a sucrose-histidine buffer solution.
>
> (4) wherein the aqueous hydration media comprises consists essentially of ammonium sulfate and sucrose and
>
> (5) the amount of aqueous hydration media used is in the range of 10 to 35 ml for each mmole of phospholipid present to form long circulating non-PEGylated liposomes.

These arguments are not persuasive. With regard to (1) and (2), applicants have mistaken since Hong teaches making a film of DSPC and cholesterol and hydrating the lipid film which implies that solvent is removed before hydration. With regard to (3), the examiner points out that the rejection is made using a combination of references and Barenholz teaches the removal of external ammonium sulfate by art known method of

dialysis. The examiner has already addressed applicant's arguments with regard to sucrose and histidine buffer and ammonium sulfate. With regard to (5) the examiner points out that Papahadjopoulos teaches hydration with 15 ml of hydration medium per millimole and Janoff teaches 25 mil of hydration medium per millimole which fall with the range of 10 to 35 ml for each millimole of the lipid. The examiner also points out that in order to obtain liposomes, the lipid film has to be hydrated totally and varying the amounts of the hydration medium is within the skill of the art. Therefore, although Hong does not teach specific hydration amounts, it is within the skill of the art to recognize that he uses enough quantities of the hydration medium to fully hydrate the lipid film. Applicants have not shown any unexpected results obtained by using specific amounts of the hydration medium.

Applicant argues that Papahadjopoulos, Janoff and Barenholz do not teach or suggest each and every element of the claimed invention and argues separately for each reference used in the rejection. In response the examiner points out that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.,* 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986). The examiner has already set forth the motivation to combine each reference for the claimed invention.

5. Claims 1-8, 10, 12, 14-22, 63-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Slater (6,355,268) in view of Janoff (4,880,635).

Instant claims are process claims. As pointed out above, instant claim 1 recites two alternatives. One of which is dissolving the phospholipids in a solvent and adding the hydration buffer to the organic solution and removing the organic solvent.

Slater discloses a process of preparation of liposome entrapped topoisomerase inhibitors. The process involves dissolving phospholipids and cholesterol in ethanol, adding an aqueous medium containing ammonium sulfate. The ammonium sulfate and ethanol were removed from the external bulk aqueous phase immediately prior to remote loading of the active agent by hollow fiber tangential flow diafiltration. The liposomes were then mixed with the drug solution containing 10 % sucrose solution. The unencapsulated drug in the bulk phase is then removed by diafiltration using exchange buffer containing 10 % sucrose and 10 millimolar Histidine, pH 6.5 (Examples 1 and 4).

What is lacking in Slater is the inclusion of sucrose and buffer in the hydrating medium.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (col. 2, line 19; col. 21, line 23 through col. 21, line 27). The phospholipids are dissolved in chloroform, evaporating chloroform and hydrating the phospholipid with a hydrating medium containing the protective sugar and a buffer. Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole) (col. 4, lines 55-66, col. 8, lines 31-47 and Example 1).

It would have been obvious to one of ordinary skill in the art to include sucrose in the hydrating medium of Slater since Janoff teaches that sucrose enables the liposomes

to retain the active agent. The use of Histidine as the buffer along with the ammonium sulfate and sucrose would have been obvious to one of ordinary skill in the art since Janoff teaches the inclusion of a buffer and Slater teaches the use of this buffer in the final liposomal preparation. Although in the method of preparation, Slater uses topoisomerase inhibitors, one of ordinary skill in the art would be motivated to use any active agent with a reasonable expectation of success. Although Slater uses a polymer containing phospholipid in the preparation of liposomes, one of ordinary skill in the art would be motivated to prepare liposomes without polymer-phospholipid since Janoff teaches that liposomes can be prepared without the use of polymer-phospholipid. Slater does not teach the encapsulation of active agents other than topoisomerase inhibitors. However, since liposomes are known to encapsulate a variety of active agents, it would have been obvious to encapsulate any active agent with a reasonable expectation of success.

Applicant's arguments have been fully considered, but are not found to be persuasive. Applicant argues that Slater teaches only one alternative recited in the claims, and even for this alternative Slater is not relevant because he needs PEGylated phospholipid in the phospholipids used for the preparing the liposomes where instant claim relates to non-PEGylated liposomes. This argument is not persuasive since applicant has not shown why one of ordinary skill in the art would not use the process of Slater could not be used for non-PEGylated phospholipids since Janoff teaches that liposomes can be prepared without polymer-phospholipids. Applicant argues that in addition, Slater shows these steps in reverse order: first doing step (b)- adding an

aqueous hydration media to phospholipids and sterol and doing step (a)-removing the solvent or mixture of solvents. This argument is confusing. As recited in instant claim 1, the phospholipids and sterol are either dissolved in a solvent or mixture of solvents and the solvent or solvents removed before adding the aqueous medium OR adding an aqueous hydration medium and then removing the solvent or solvents. Slater as pointed out above teaches dissolving phospholipids and cholesterol in ethanol, adding an aqueous medium containing ammonium sulfate. Ethanol was removed from the external bulk aqueous phase immediately prior to remote loading of the active agent. ***In what way this is in reverse order?***

Applicant argues that in Slater, the ammonium sulfate and ethanol were removed from the external bulk aqueous phase immediately prior to remote loading of the active agent by hollow fiber tangential flow diafiltration and that this step is clearly different than the claimed process. This argument is not persuasive since as pointed out above, instant claim 1 does not recite the presence of any active agent.

Applicant argues that in the above step the claimed process removes only the organic solvent, whereas Slater process removes both ammonium sulfate and ethanol together by tangential flow diafiltration. Therefore, according to applicant, Slater does not teach or suggest the claim element of “removing ammonium sulfate from extra liposomal hydration medium by dialysis using a sucrose-histidine buffer.

This argument is not persuasive. According to instant claim 1, the steps are dissolving the phospholipids and sterols in a solvent, adding the hydration medium and removing the solvent and removing ammonium sulfate from the extra liposomal

ammonium hydration medium by dialysis. Slater teaches removal of both solvent and the extra liposomal ammonium sulfate in a single step, that is, using the technique of diafiltration (Slater clearly states in example 1 that the liposomes contain ammonium sulfate within the interior aqueous compartment which implies that only external ammonium sulfate is removed) whereas applicant removes the solvent and then the ammonium sulfate by dialysis. The dialysis process of removing substances is well known in the art of biological sciences and whether the solvent and external ammonium sulfate are removed in two separate steps or using one step as in Slater, the result is the same and applicant has not shown any unexpected results obtained by manipulating the process step of removing the solvent and ammonium sulfate taught by Slater. In this context, the examiner points out to col. 11, lines 55-61 which clearly indicates that Slater is aware of removing small molecular weight compounds such as drugs by dialysis. Contrary to applicant's arguments, Slater does teach the use of ***exchange buffer*** containing 10 % sucrose and 10 millimolar histidine, pH 6.5 though not using dialysis as the technique. Applicant's arguments that in instant process, the therapeutic or diagnostic agent is taken in a sucrose-histidine buffer whereas in Slater the therapeutic drug or diagnostic drug is taken in sucrose solution are not persuasive since instant claim 1 does not even recite the presence of a drug. Furthermore, the choice of a buffer and pH depends upon the drug stability at a particular pH and it is within the skill of the art to use a suitable buffer along with sucrose taught by Slater. Applicant has not shown any criticality of histidine buffer.

Applicant's arguments that Slater does not teach the hydration media of ammonium sulfate and sucrose are not persuasive sine Janoff teaches the importance of sucrose both inside and outside the liposomes and therefore, one of ordinary skill in the art would be motivated to include sucrose in the ammonium sulfate taught by Slater.

Applicant argues that it is well known that NaCl and HEPES buffer gives stable liposomes and that Janoff shows that addition of sucrose to NaCl and HEPES buffer overcomes the destabilization during dehydration and rehydration. Applicant therefore, questions as to who one of ordinary skill in the art know that when sucrose with sodium or potassium buffer and HEPES in hydration medium, which is shown by Janoff to help in protection from leakage of active material from the liposome in which it is entrapped during dehydration and rehydration process, would also help in such protection even when the hydration medium comprises essentially sucrose and ammonium sulfate.

This argument is not persuasive. First of all, nowhere in the specification Janoff states that NaCl and HEPES buffer are critical. In fact, Janoff states on col. 4, lines 55-66 that the liposomes can be prepared by adding aqueous solution to hydrate the lipid film; if NaCl and HEPES buffer are critical, then Janoff would have certainly stated that hydration must be done using this buffer and not made a generic statement of 'aqueous solution". Secondly, it is very clear to anyone reading Janoff's patent that it is the protective sugar which is critical and not the buffer. It should be pointed out that the motivation to include sucrose need not be same as applicant's. With regard to applicant's arguments that the examiner states that in Janoff the phospholipids are dissolved in chloroform, which is then evaporated and the lipid hydrated with a hydrating

medium containing the protective sugar and a buffer and that there is no such statement from Janoff, the examiner points out col. 8, lines 40-58 of Janoff which clearly teach the inclusion of sugar in hydrating medium. Applicant is incorrect in stating that there is no reasoning or motivation to pick only sucrose from a laundry list of sugars in Janoff. In column 5, Janoff states that among disaccharides, trehalose and sucrose are most effective (lines 63 and 64) and in Example 4, Janoff teaches vesicles containing sucrose).

6. Claims 1-8, 10, 12, 14-22 and 63-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Forssen (5,714,163) in combination with Janoff (4,880,635) and Papahadjopoulos (4,235, 871), optionally in further combination with (Slater (6,355,268) and/or Clerc (5,939,096).

Instant claims recite two alternatives: the organic solvent is removed before or after the hydration. That means the hydration is performed on a dried lipid film or in a solution of the lipids in the organic solvent.

Forssen discloses a method of preparation of liposomes wherein the spray dried lipid mixture containing DSPC and cholesterol is hydrated with ammonium sulfate. Since it is a lipid mixture dissolving the lipids in an organic solvent for spray-drying is implicit (Example 1). Although Forssen teaches the use of 300 mM sucrose for hydration medium, he does not teach the use of hydration buffer containing both ammonium sulfate and sucrose. It is unclear whether in Forssen, the hydrating sucrose solution is in a buffer. The liposomes in Forssen are then subjected to buffer change

using 300 mM sucrose. The removal of ammonium sulfate in this step thus, is implicit in Forssen.

Forssen however, does not teach the hydration of the lipid using ammonium sulfate, Sucrose and histidine.

Janoff teaches that sugars such as sucrose when present both inside and outside would enable the liposomes to retain Adriamycin during dehydration and rehydration (col. 2, line 19; col. 21, line 23 through col. 21, line 27). The phospholipids are dissolved in chloroform, evaporating chloroform and hydrating the phospholipid with a hydrating medium containing the protective sugar and a buffer. Janoff further teaches the hydration of the 80 micromoles of lipid with 2 ml of buffer (25 ml per mmole) (col. 4, lines 55-66, col. 8, lines 31-47 and Example 1).

Papahadjopoulos discloses methods of formation of liposomes. The methods involve either removal of the organic solvent before hydration (Example 1) or making an emulsion using an organic solvent containing phospholipid and an aqueous medium and evaporating the organic solvent (Example 2). In either method, the amount of the lipid is 100 micromoles and the aqueous medium added is 1.5 ml which corresponds to 15 ml of aqueous medium per millimole of the phospholipid and the hydration medium contains histidine.

Slater discloses a process of preparation of liposome entrapped topoisomerase inhibitors. The process involves dissolving phospholipids and cholesterol in ethanol, adding an aqueous medium containing ammonium sulfate. The ammonium sulfate and ethanol were removed from the external bulk aqueous phase immediately prior to

remote loading of the active agent by hollow fiber tangential flow diafiltration. The liposomes were then mixed with the drug solution containing 10 % sucrose solution. The unencapsulated drug in the bulk phase is then removed by diafiltration using exchange buffer containing 10 % sucrose and 10 millimolar Histidine, pH 6.5.

What is lacking in Slater is the inclusion of sucrose and buffer in the hydrating medium.

Clerc while disclosing a drug loading method into the liposomes teaches the hydration of the phospholipids with a solute species which is saline or a disaccharide (sucrose) and a buffer which is the same as the internal or external aqueous medium such as histidine or MES or Tris (col. 7, lines 5-15; col. 8, lines 1-15).

It would have been obvious to one of ordinary skill in the art to include sucrose and histidine in Forssen since Janoff teaches that sucrose protects the liposomes during the dehydration/rehydration process and Papahadjopoulos teaches the routine practice of the inclusion of histidine in the hydration buffer. One of ordinary skill in the art would be motivated further to include both sucrose and histidine in the hydrating medium since both Slater and Clerc teach the use of this combination in the liposomal preparations.

Applicant's arguments have been fully considered, but are not found to be persuasive. In essence, applicant argues that Forssen teaches several counter ions and that the examiner has not explained why one skilled in the art looking at Example 1 of Forssen would choose sulfate as the counter ion especially when there are other ions giving entrapment above 67 %. Applicant points out col. 7, lines 26-32 of Forssen

(tumor data) and argue that notably from this passage, sulfate is not at all used, which clearly shows that the inventors did not think that sulfate was useful.

This argument is not persuasive; Forssen for whatever reasons does not test the liposomes containing Vcr and ammonium sulfate since col. 7, lines 26-29 indicate the testing of only 9 groups. Applicant's arguments would have been persuasive to some extent if Forssen tested the liposomes containing sulfate as the counter ion along with other counter ions and found that this counter ion is less effective compared to others. The lines on col. 7 clearly indicate that this group was not tested at all. Therefore, applicant's arguments that the inventors did not think that sulfate was useful is incorrect. Secondly, Instant claims are process claims and do not even recite an active agent. Third, Forssen does teach ammonium sulfate among a short list of compounds in the process of preparation as evident from Table 1 on col. 7 and the reference of Slater clearly teaches the use of ammonium sulfate in the process. The examiner again points out that instant claims are process claims and not method of tumor treatment. Finally, it should be pointed out that the prior art is suggestive of the use of ammonium sulfate and other ammonium salts and applicant has not provided any comparative data showing that the use of ammonium sulfate leads to unexpected results compared to other ammonium salts.

Applicant argues that the examiner misread Clerc when he states “while disclosing a therapeutic or diagnostic agent loading method into the liposomes teaches the hydration of the phospholipids with a solute species which is saline or a disaccharide (sucrose) and a buffer which is the same as the internal or external

aqueous medium such as histidine or MES or Tris (col. 7, lines 5-15; col. 8, lines 8-15). According to applicant, Clerc does not teach or suggest the element of claim 1 of 'removing ammonium sulfate from extra liposomal hydration medium by dialysis using sucrose-histidine buffer solution as the 'buffers used in Clerc are instead used to form liposomal pH gradient.

These arguments are not persuasive. The examiner disagrees with applicant since the examiner only stated what was taught by Clerc on columns 7 and 8. These locations clearly teach buffers which can be used and solutes which can be used. The pH gradient taught by Clerc is for loading the drug and instant claims do not exclude a pH gradient to load a drug.

Applicant's arguments that the present invention provides a unique process of making a liposome that resulted in a unique property of increasing half circulation period of the liposome so prepared having at least 25 times longer than that the conventional non-liposomal preparations are not persuasive. The rejections are made using a combination of references which teach process of preparation of liposomal preparations; ***therefore, to show unexpected results one should compare the liposomes of the prior art with liposomes produced by instant process and not with a conventional non-liposomal preparation.*** The examiner has not used any reference which shows conventional drug preparation in the combination of references used. In medical field, many drugs are administered as free drugs in solution and since liposomes are sustained release vehicles (meaning the drug is released slowly) common sense dictates that the drug encapsulated in liposomes lasts longer in

circulation than the drug in a solution form. Applicant has not shown the criticality of sucrose or histidine as the buffer or the use of ammonium sulfate or combination of these which the prior art clearly teaches their routine use in the preparation of liposomes.

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

7. THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gollamudi S. Kishore, Ph.D whose telephone number is (571)272-0598. The examiner can normally be reached on 6:30 AM- 4 PM, alternate Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Krass Frederick can be reached on (571) 272-0580. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Gollamudi S Kishore /
Primary Examiner, Art Unit 1612

GSK